REMARKS

Amendments to the Claims

Claims 1-5, 7-10, 21-25, 27-30, 60, 70, 89 and 91 are pending in the application prior to this amendment.

Claim 7 is being canceled without prejudice.

Claims 1, 21, 60, 70, 89, and 91 are being amended. Claims 1, 21, 70 and 89 are amended to recite that the anti-resorptive agent (ARA) is a highly specific cytokine antagonist comprising a monoclonal antibody that inhibits TNF-α. Claim 60 is amended to recite that the anti-resorptive agent comprises a monoclonal antibody that inhibits TNF-α. Support for this amendment can be found in the Specification, for example, at page 28, lines 24-26; at page 29, line 28 through page 30, line 14; and Examples I through IV at page 60, line 14 through at page 63, line 19.

Claim 91 is being amended to recite that the "anti-resorptive agent comprises REMICADE® infliximab." Support for this amendment can be found in the Specification, for example, at page 35, lines 11-19.

New Claim 92 is being added. Support for this claim can be found in the Specification, for example, at page 28, lines 24-26; at page 29, line 28 through page 30, line 14; at page 35, lines 11-19; and Examples I through IV at page 60, line 14 through at page 63, line 19.

No new matter has been added. Entry of the amendments is requested.

Status of Claim 91

According to the Examiner, "Claim 91 has been withdrawn from consideration since applicant has constructively elected estrogen as highly specific cytokine antagonist that inhibits TNF-alpha" (the Office Action at page 2). Applicants respectfully disagree.

Notwithstanding the Examiner's statement, Applicants have not constructively elected estrogen. In the previous Amendment, the independent claims had been amended to recite that the "anti-resorptive agent" is a "highly specific cytokine antagonist that inhibits TNF-α." In the present Amendment, the claims are amended to recite that the "highly specific cytokine antagonist" comprises a "monoclonal antibody." Although it is an anti-resorptive agent, estrogen is neither a "highly specific cytokine antagonist" (HSCA) nor a "monoclonal antibody." As

discussed further in detail below, an HSCA specifically refers to an antagonist that inhibits only the specific cytokine(s) of interest (the Specification at page 8, lines 16-19). Estrogen is believed to block more than one cytokine and is not believed to be an HSCA. Further, estrogen is a small molecule, not an antibody. Therefore, Claim 91, particularly as amended and directed to an HSCA monoclonal antibody (*e.g.*, REMICADE® infliximab), should not be withdrawn, but should be pending. For clarification, Claim 7 drawn to "estrogen" is being canceled. Correction is respectfully requested.

Rejection of Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 Under 35 U.S.C. § 112

Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 have been rejected under 35 U.S.C. § 112 for allegedly lacking enablement for methods of treating uncoupled resorbing bone or osteoporosis comprising administration of a highly specific cytokine antagonist. The Office Action states that: "the specification, while being enabling for treating an uncoupled resorbing bone or osteoporosis comprising administration of highly specific cytokine antagonist that inhibits TNF-α such as estrogen, does not reasonably provide enablement for all other high specificity cytokine antagonists" (the Office Action, bridging paragraph between page 2 and 3).

As noted in the Manual of Patent Examining Procedure, 8th Ed., Rev. 6 (Sept. 2007) (MPEP) at § 2164.03, even the presence of only one working example should never be the sole reason for rejecting a claim as being broader than the enabling disclosure. Further, "for a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." *Id.*

Notwithstanding the statement in the Office Action, the Examples in the present Specification pertain to the use of REMICADE® infliximab, a monoclonal antibody that binds and inhibit TNF-α, not to the use of estrogen (see the Specification at page 60, line 15 through page 63, line 23). REMICADE® infliximab differs from estrogen in number of ways. First, REMICADE® infliximab is a protein peptide comprising a monoclonal antibody, whereas estrogen is a molecule in the form of steroid. Further, while estrogen can block TNF-α and other cytokines, it is not a *highly specific* cytokine antagonist. As described in the present

specification, a highly specific cytokine antagonist such as a monoclonal antibody HSCA "bind[s] specifically to a certain target protein and essentially no other proteins" (page 24, lines 24-26). The Specification teaches that estrogen is believed to "block the production of pro-inflammatory cytokines" (the Specification at page 3, lines3-8). Applicants respectfully request reconsideration of the enablement requirement based on consideration of the examples directed to the use of REMICADE® infliximab, not the use of estrogen.

Independent Claims 1, 21, 60, 70 and 89 have been amended to recite that the anti-resorptive agent comprises a monoclonal antibody that inhibits TNF-α (emphasis added). This amendment to the independent claims is made to reflect that the anti-resorptive agent is a monoclonal antibody and does not embrace any small molecule such as estrogen.

Further, as noted by the Examiner, the level of skill in the art was extremely high at the time the invention was made (the Office Action at page 4). The knowledge in this art at the time the invention was made was also extensive. In *In re Wands*, the court stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'" (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)). At the time the invention was made, methods for producing monoclonal antibodies were well known and widely practiced. In fact, the Specification provides numerous monoclonal antibodies against TNF-α which can be used in the present invention and which were readily available to one of skill in the art at the time the invention was made (see the Specification at page 29, line 28 through page 30, line 4; and at page 31, line 5 through page 32, line 27). Further, the Specification sufficiently exemplifies how to administer a bone forming agent in combination with a HSCA (*e.g.*, REMICADE® infliximab) into an uncoupled resorbing bone (Examples I through IV in the Specification at page 60, line 15 through page 63, line 19). Moreover, throughout the Specification, the desirable effects of the present invention on the uncoupled resorbing bone are well described.

Considering what was well-known in the art and the teachings of the present application, including the detailed discussion of a monoclonal antibodies that inhibit TNF-α, and the very high level of skill in the art, one of skill in the art would be able to practice the claimed method without engaging in undue experimentation. Therefore, the rejected claims, particularly as amended, are enabled for treating an uncoupled resorbing bone by administering a bone forming agent in combination with a highly specific cytokine antagonist comprising a monoclonal antibody that inhibits TNF-α. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 Under 35 U.S.C. § 112

Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 have been rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for recitation of the term "highly." The Office Action states that: "Recitation of the term highly in claims 1, 21, 70 and 89 renders the claim indefinite. The term is [a] relative term" (the Office Action at page 5, third paragraph). Applicants respectfully traverse the rejection.

The Manual of Patent Examining Procedure (MPEP) § 2173.05(b) states the following:

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. (MPEP §2173.05(b); emphasis added)

The Specification recites:

> Second, since the high specificity cytokine antagonist (HSCA) inhibits only the specific cytokine(s) of interest, the HSCA may be combined with other therapeutic agents (such as bone growth agents, *e.g.*, FGF or mesenchymal stem cells) that can also be injected into the bone without reducing the effectiveness of those other agents. (the Specification at page 8, lines 16-19; emphasis added)

The scope of the high specificity cytokine antagonist or highly specific cytokine antagonist is defined in the specification as shown above. The term "high specificity" or "highly specific," therefore, pertains to a functionality in which the antagonist inhibits only the specific cytokine(s) of interest. As noted above, the level of skill in the art was

extremely high at the time the invention was made (the Office Action at page 4). One of ordinary skill in the art would understand the scope of the term "highly specific" based on the teachings in the present Specification as required by the MPEP § 2173.05(b). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 Under 35 U.S.C. § 103(a)

Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 have been rejected under 35 U.S.C. § 103(a) for being unpatentable over Radomsky (U.S. Patent No.: 5,942,499; hereinafter "Radomsky") in view of Cullis-Hill (U.S. Patent No.: 6,593,310; hereinafter "Cullis-Hill") and Boyle *et al.* (U.S. Patent Publication 2003/0207827; hereinafter "Boyle") and further in view of Trieu *et al.* (U.S. Patent Publication 2002/0026244; hereinafter "Trieu").

According to the Examiner, Radomsky teaches a composition for promoting bone growth. The composition comprises growth factors such as fibroblast or platelet-derived growth factor (col. 1, lines 19, 35-36, and 61). These compositions can be administered at the site of desired bone growth including vertebral compression fractures and in pathological bond defects associated with osteoporosis (col. 2, lines 50-58).

According to the Examiner, Cullis-Hill teaches a method of treating osteoporosis with a compound such as pentason polysulfate, and teaches estrogen as an anti-resorptive agent which reduces bone fractures. As discussed above, the independent claims have been amended to recite "a monoclonal antibody." Cullis-Hill, which teaches estrogen as an anti-resorptive agent, does not apply to independent Claims 1, 21, 60, 70 and 89, particularly as amended, because estrogen, as discussed above, is neither a HSCA nor a monoclonal antibody.

According to the Examiner, Trieu teaches nucleus pulposus implants that are resistant to migration and a method involved in implanting them. Specifically, the method is directed to removal of the natural nucleus pulposus of the intervertebral disc and placement of a nucleus pulposus implant. Trieu teaches that nucleus pulposus implants can deliver growth factors which would repair annulus fibrosis and the endplates of the disc (see Trieu, paragraph [0101] and [0102]).

According to the Examiner, Boyle teaches a method of treating bone diseases including osteoporosis with osteoprotegerin (OPG), a member of the tumor necrosis factor receptor (TNFR) superfamily involved in the regulation of bone formation. Boyle teaches that OPG acts

as a soluble receptor of the TNF family and may prevent a receptor-ligand interaction involved in the osteolytic pathway. Boyle does not teach that OPG inhibits TNF-α. Nor does it teach a monoclonal antibody that inhibits TNF-α.

The combination of the references of record does not render obvious the present invention because it does not teach all elements in the independent claims, particularly as amended. According to the Manual of Patent Examining Procedure (MPEP), all of the claim limitations must be taught to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03 citing, *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). None of the references, alone or in combination, teaches use of a highly specific cytokine antagonist that inhibits TNF-α. Further, independent Claims 1, 21, 60, 70 and 89 as amended require the recited anti-resorptive agent to comprise a monoclonal antibody that inhibits TNF-α. Because the combination of the references of record does not teach all elements in the independent claims, particularly as amended, a *prima facie* case of obviousness has not been established and the combination of the references does not render obvious the claimed invention.

Further, the Office Action states that "Radomsky, Cullis and Boyle do not teach the administration of the formulation into the bone" (the Office Action page 7, third paragraph). Trieu does not compensate for this deficiency. As discussed above, the teaching of Trieu is limited to administration of a formulation from a nucleus pulposus implant placed in between two vertebral bones. The method first requires the placement of an implant between two vertebrae. Particularly, the Examiner characterizes this type of administration as "local administration in between bones" (the Office Action at page 8, last sentence of the first paragraph). It is clear that local administration by releasing a formulation from an implant placed in between two bones (*i.e.*, two vertebrae) is not the same type of administration as one that requires administering the formulation into the bone. Accordingly, Trieu does not compensate the deficiency of Radomsky, Cullis-Hill and Boyle. Therefore, a *prima facie* case of obviousness is not established in view of these references of record.

Moreover, the Office Action states that: "One skilled in the art would have been motivated to administer in to the bone the formulation...because Trieu et al. successfully teach local administration of drug in between bones in order to treat osteoporosis" (the Office Action at page 8, second paragraph). Applicants respectfully submit that one of ordinary skill in the art

would not have been motivated to administer the claimed formulation into the bone based on a prior art reference that merely teaches that a therapeutic agent can be administered from a local implant placed between two bones. The advantages one can achieve from administration of the formulation directly *into the bone* over other types of local administrations, such as those described in Trieu, are significant, but not easily recognized by one of ordinary skill in the art. Osteoporosis involves the progressive resorption of bone which requires long-term treatment throughout the resorptive process. The present Specification specifically teaches about the need for long term administration in treating osteoporosis[1] and the direct advantages of administering the formulation into the bone in such treatment. The Specification provides that: "[S]ince the cortical shell of the bone comprises a relatively dense structure, this outer component of the bone may prevent the out-diffusion of the drug and so may provide a suitable depot for the osteotherapeutic drug, thereby increasing its half-life in the target bone" (the Specification at page 7, lines 14-17). The Specification teaches about the difference in half-life of REMICADE® infliximab if it were to be administered systemically versus directly into the bone (about 1 week *vs.* about 9 weeks).[2] Trieu does not contemplate this advantage because Trieu's method is only limited to administering a formulation from a disc implant placed between two vertebral bones (*i.e.*, in the intervertebral space). Further, the present Specification also provides that, in addition to significantly increasing the potency and half-life of the formulation, one can also reduce the level of unwanted side effects of long-term therapy by keeping the formulation from diffusing outside of the target bone.[3]

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[1] "Because the osteoporosis ("OP") involves the progressive resorption of bone in which many factors are involved, in many instances, simply providing a single dose or even a regimen over the space of a few days may not be sufficient to manage the OP...Accordingly, it is desirable for the AR and/or BF agent to remain within the bone as long as possible in a pharmaceutically effective amount" (the Specification at page 39, line 26 through page 40, line 1).

[2] "For example, suppose a clinician administered 0.3 ml of 60 mg/ml REMICADE® infliximab into a 2.7 cc bone, thereby producing an infliximab concentration in the bone of about 6 mg/ml, or 6 parts per thousand. Without wishing to be tied to a theory, if infliximab has the same half-life within a bone as it does when administered systemically (*i.e.*, about 1 week), then the concentration of infliximab would remain above about 10 ppm for about 9 weeks. Therefore, if another dose were needed, the clinician would only need to provide the second dose after about two months" (the Specification at page 45, lines 16-29).

[3] "For example, if it is believed that a BF and/or AR agent is effective when present in the range of about 1-10 mg/kg or 1-10 ppm (as is believed to be the case for the TNF antagonist REMICADE® infliximab as an AR agent), and since the cancellous portion of a cervical vertebral body has a volume of about 3 ml (or 3 cc or 3g), then only about 3-30 μg of the HSCA would need be administered to the bone in order to provide a long lasting effective amount of the drug. The small amounts available by this route reduce the chances of deleterious side effects of the BF and/or AR agent" (the Specificification at page 45, lines 15-21; emphasis added).

Moreover, neither Trieu nor any other reference of record teaches or suggests the significance of long-term treatment for osteoporosis. It should also be noted that the teachings of Trieu focus only on repairing physical damage to the disc (see Trieu page 9, paragraphs [0101] and [0102]). Such physical damage may include a surgical incision made to the annulus fibrosis during the nucleus pulposus implantation procedure and can be repaired with a rather short-term treatment that promotes the healing process. On the other hand, bone damage caused by osteoporosis as described in the present Specification may require at least 1 month to 6 or 12 months or an even longer time to reverse the resorptive process and to restore the bone forming process (see the Specification at page 16, lines 15-23 and pages 39 through 40, bridging paragraph). One of ordinary skill in the art would *not* have been motivated to combine the teachings of Trieu and the other references to arrive at the claimed invention, namely administration of the formulation into the bone.

In summary, the claimed invention would not have been obvious to the one of ordinary skill in the art because a *prima facie* case of obviousness has not been established and because the one of ordinary skill in the art would not have been motivated to combine the teachings of the references of record to arrive at the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No.: 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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